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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/762,966	SCHUETZ ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-12* is/are pending in the application.

4a) Of the above claim(s) *4-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 7-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/21/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of species A of target nucleic acid in the reply filed on August 24, 2006 is acknowledged. Applicants traverse the requirement for election of species of chronic illness on the ground(s) that these species overlap in scope. This is found persuasive and the requirement is withdrawn.

2. Claims 4-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 24, 2006.

3. Claims 1, 3 and 7-12 will be examined.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on January 21, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

5. The disclosure is objected to because of the following informalities: the first paragraph has not been updated with respect to the status of the parent application.

6. The disclosure is objected to because of the following informalities: it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The hyperlink is present on page 23, line 22.

Appropriate correction is required.

Drawings

7. The drawings are objected to under 37 CFR 1.83(a) because they fail to show SEQ ID NOs for sequences in Fig. 1, as described in the specification. The figure legend of Fig. 1 refers to SEQ ID NO: 1-9, but since these SEQ ID NOs are not present in the figure, it is not clear which sequence is SEQ ID NO: 1, 2, etc. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention,

(5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claim 8 is drawn to the method of detecting the presence of target RNA in acellular biological sample obtained from an animal suspected of suffering from a chronic illness, claim 9 is drawn to the method of claim 8 where the illness is a spongiform encephalopathy, and claim 10 is drawn to the method of claim 9 where the spongiform encephalopathy is bovine spongiform encephalomyelitis, the method comprising providing the acellular sample, contacting the sample with a nucleic acid probe which specifically hybridizes to target RNA molecule that comprises sequences transcribed from the animal's germline DNA, and detecting a hybridization complex comprising the nucleic acid probe as indicative of the presence of the target RNA molecule in the acellular biological sample. The specification recites that the present invention can be used to detect spongiform encephalopathies, such as BSE (page 2, lines 27, 28). However, there is no support in the specification or prior art for detection of spongiform encephalopathies, such as BSE by detection of germline RNA in acellular samples, which by Applicants' definition, are plasma, serum, urine, milk, saliva, sweat, tears, phlegm, cerebrospinal fluid, semen, feces, etc. (page 4, lines 6-10).

The state of the prior art

The specification provides description of detection of 18S rRNA in normal fetal bovine serum, horse serum and goat serum, using 18S rRNA primers (page 22). The specification also provides description of an experiment involving two cows: one healthy and one with confirmed diagnosis of BSE. Total RNA was extracted from serum of both of these samples, cloned and sequenced. The healthy cow RNA contained three sequences for which no significant homologies

were found in a nucleotide database, and RNA from the BSE-infected cow contained four sequences for which no significant homologies were found in a nucleotide database (pages 23 and 24). There is no comparison of the unique sequences found in the healthy and BSE cow, and no correlation between the BSE and the obtained RNA sequences.

However, as indicated by the prior art (van Keulen et al., The Veterinary Quarterly, vol. 22, pp. 197-200, October 2000), detection of encephalopathies, and BSE in particular, is based on the detection of the modified prion protein, PrP, in the brain of affected animals, using either PrP-specific antibodies, partial resistance of PrP to protease or enhancement of immunoreactivity of PrP by denaturation (page 199, fourth paragraph). Other detection methods include histopathology, immunohistochemistry and Western blotting (page 199, first and second paragraph).

No evidence has been found that DNA fragmentation, as caused by apoptosis, is linked to BSE (see Theil et al., J. Comp. Pathol., vol. 121, pp. 357-367, 1999), or that RNA is released from the affected cells. As indicated by Thiel et al., in situ end-labeling (ISEL) was applied to brain tissue samples from BSE cows (page 358, paragraphs 2-6). The ISEL-labeled cells were found in areas of spongiform morphology, but also in grey matter lacking spongiform changes, and these cells did not show any features of apoptosis (page 360, the last paragraph; page 362). The authors concluded that even though nuclear fragmentation does occur in brains of BSE-affected animals, it was not certain whether it was caused by apoptosis (page 365, the last paragraph).

Even if RNA or DNA associated with BSE were to be found in the brain of affected cows, it is not clear how they could be detected outside of the brain, in plasma or serum, since nucleic acids cannot cross the brain-blood barrier (see The New Encyclopedia Britannica, 15th Edition, vol. 25, p. 912, 1994).

Finally, it is not certain that the PrP protein is the cause of BSE. As evidenced experimentally by Bastian (U.S. Patent No. 6,033,858), BSE might be caused by spiroplasma (col. 7, lines 56-67; col. 8, lines 1-67; Fig. 4), and detection of encephalopathies may be accomplished by detecting the 16S rRNA of spiroplasma in acellular samples (Examples I-VI).

Quantity of Experimentation

The quantity of experimentation in this case is extremely large. One would have to perform a study relating germline RNA found in acellular samples to any of animal chronic diseases, including encephalopaties, and, in particular, to BSE. This would involve a investigating statistically significant number of cows infected with BSE and healthy animal controls to determine which of the RNA fragments detected in serum or plasma of these animals were associated with the presence of the disease. This step would involve cloning of total RNA from all of the animals, sequencing the RNA, and determining which sequences were uniquely associated, in statistically significant manner, with BSE. Additionally, these sequences would need to be checked for the presence of viral or bacterial sequences which might have gotten incorporated into germline DNA. The second step would require investigation of the connection between the level of progression of the disease and the presence of certain RNA fragments in the acellular samples. Again, this step would necessitate investigation of statistically significant numbers of animals at different levels of BSE progression as compared to healthy controls. The steps of total RNA extraction, cloning, sequencing and association of certain sequences with the disease, would have to be repeated for these groups of animals. This would require years of inventive effort, with each of the many intervening steps, without a guarantee of success in the succeeding steps.

Working Examples

The specification provides only an example of sequencing total RNA obtained from one healthy cow and one BSE-infected cow. The healthy cow's RNA contained three sequences for which no significant homologies were found in a nucleotide database, and RNA from the BSE-infected cow contained four sequences for which no significant homologies were found in a nucleotide database (pages 23 and 24). There is no comparison of the unique sequences found in the healthy and BSE cow, and no correlation between the BSE and the obtained RNA sequences.

Guidance in the Specification

The specification provides no evidence that the unique RNA sequences obtained from the healthy and BSE-infected cows are indeed germline sequences, nor does it provide evidence that the sequences unique to the BSE cow are different from the sequences unique to the healthy cow. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. There is no support for the connection between the presence of certain RNA sequences in the serum of BSE-infected cow. There is no evidence of statistically-significant correlation between the presence of certain RNA sequences in serum of BSE-infected cows with the presence of the disease, and with the severity of the symptoms. The prior art fails to show enablement for teaching of possibility of detecting BSE by detection of germline RNA in acellular samples.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the fact that encephalopathies, such as BSE, are detected based on histopathological or antibody-protein interactions evidence, coupled with the fact

of impermeability of blood-brain barrier to nucleic acids and lack of evidence of cell apoptosis in BSE-infected animals, indicates that a skilled artisan would need to perform a large amount of undue experimentation to even establish a connection between the presence of certain germline RNA sequences circulating in the blood and the presence of BSE infection in an animal.

Due to the large quantity of experimentation necessary to establish a connection between circulating germline RNA in animals infected with BSE, the lack of guidance presented in the specification regarding a connection between circulating germline RNA in animals infected with BSE, the absence of working examples directed to a connection between circulating germline RNA in animals infected with BSE, the state of the prior art (see discussion above), the high skill level in the art, undue experimentation would be required of the skilled artisan to make and use the claimed invention.

Claim interpretation

10. According to Applicants' definition, an "acellular biological sample" is plasma, serum, urine, milk, saliva, sweat, tears, phlegm, cerebrospinal fluid, semen, feces, etc. (page 4, lines 6-10).

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 3, 7, 8, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Kopreski (WO 97/35589; cited in the IDS).

Regarding claim 1, Kopreski teaches detecting the presence of a target RNA molecule in acellular biological sample from an animal (Abstract), the method comprising:

providing the acellular biological sample (Kopreski teaches providing plasma or serum sample (page 2, lines 17-30; page 12, lines 5-16).);

contacting the sample with a nucleic acid probe which specifically hybridizes to target RNA molecule that comprises sequences transcribed from the animal's germline DNA (Kopreski teaches contacting the sample with primers which specifically bind to tumor-derived or tumor-associated RNA (page 16, lines 33, 34; page 17; page 18, lines 1-12).);

detecting the hybridization complex comprising the nucleic acid probe as indicative of the presence of the target RNA molecule in the acellular biological sample (Kopreski teaches detection of amplification products (page 23, lines 17-34; page 24; page 25, lines 1-4).)

Regarding claim 3, Kopreski teaches rearranged germline DNA (page 21, lines 7-9, 17-19, 22-30).

Regarding claim 7, Kopreski teaches serum and plasma (page 2, lines 17-30; page 12, lines 5-16).

Regarding claim 8, Kopreski teaches sample obtained from animal suffering from cancer (page 1, lines 20-23; page 2, lines 17-20).

Regarding claim 11, Kopreski teaches amplification of the target RNA molecule (page 6, lines 1-29; page 10, lines 4-28; page 16, lines 15-32).

Regarding claim 12, Kopreski teaches RT-PCR (page 6, line 9; page 10, line 20; page 16, line 19).

13. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
11/8/06